



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Griffin and Zlokovic Art Unit: 1647
Application No.: 09/777,484 Examiner: B. Bunner
Filed: February 5, 2001
Title: NEUROPROTECTIVE, ANTITHROMBOTIC, AND
ANTI-INFLAMMATORY USES OF ACTIVATED PROTEIN C (PROTEIN C (APC))

#10
MQJ
4/22/03

Commissioner of Patents
Washington, D.C. 20231

DECLARATION OF
APPLICANT UNDER 37 C.F.R. § 1.132

Sir:

We, John H. Griffin and Berislav Y. Zlokovic, co-inventors of the above-identified application, do hereby declare and state that:

1. We are familiar with the above-identified patent application and the disclosure in the Specification of neuroprotective, antithrombotic, and anti-inflammatory uses of activated protein C (APC).

2. We have reviewed the Office Action mailed October 7, 2002, and understand that claims 1-16 and 19-21 have been rejected, *inter alia*, under 35 U.S.C. 112, first paragraph, for allegedly lacking enablement. We understand that the Examiner has alleged that the specification, while being enabling for methods for decreasing brain infarction volume and edema volume in a subject, does not provide enablement for methods of protecting neuronal cells from cell death in a subject having or at risk of having a neuropathological disorder. We further understand that the Examiner has alleged that the specification is allegedly not enabling for a method of reducing inflammation in a subject having or at risk of having a neuropathological disorder.

3. We have demonstrated and explicitly set forth in the present specification (see Examples 1 and 2) that treatment with protein C (APC) either before or after induction of stroke protected mice from accelerated stroke-related death and restored cerebral blood flow during middle cerebral artery occlusion (see specification, pages 30-31). In addition, we have demonstrated and explicitly set forth in the present specification that administration of protein C (APC) reduced volumes of brain infarction and edema by 59% and 50%, respectively (see, e.g., page 10, lines 3-4; page 31, lines 18-24; page 33, lines 22-26).

4. Moreover, as set forth in Exhibits A and B accompanying this Declaration, we have demonstrated that protein C (APC) is indeed directly neuroprotective. For example, in Exhibit A, we demonstrate that protein C (APC) directly activates anti-apoptotic pathway in ischemic brain endothelial cells through protease activated receptor-1 (PAR-1) and endothelial protein C (APC) receptor (EPCR).

5. In Exhibit B, we have demonstrated that protein C (APC) reduces N-methyl-D-aspartate (NMDA)-induced apoptosis in mouse cortical neurons by blocking tumor suppressor protein p53, normalization of the proapoptotic *Bax/Bcl-2* ratio and reduction in caspase-3 signaling. Moreover, we have demonstrated that protein C (APC)'s neuroprotective effects on cortical neurons and prevention of NMDA excitotoxicity in mice *in vivo* require PAR-1 and PAR-3 on neurons. Thus, protein C (APC) can be used as a direct neuroprotective agent.

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6. We further declare that all statements made herein of knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

April 4, 2004

Date

April 4, 04

Date

John H. Griffin

John H. Griffin

Berislav V. Zlokovic

Berislav V. Zlokovic

Attachment: Exhibits To Declaration (A and B)